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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/047,652	03/25/1998	VASSILIOS PAPADOPOULOS	009/064/SAP	3470
21186	7590	07/12/2006	EXAMINER	
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A. P.O. BOX 2938 MINNEAPOLIS, MN 55402			DAVIS, MINH TAM B	
			ART UNIT	PAPER NUMBER
			1642	
DATE MAILED: 07/12/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/047,652	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on April 19, 24, 25, 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-55, 58-60, 63, 64, 66-68, 70, 72-74, 78, 79, 81 and 82 is/are pending in the application.
- 4a) Of the above claim(s) 58-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-55, 63, 64, 66-68, 70, 72-74, 78, 79, 81 and 82 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>05/04/06: 04/25/06</u> . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>02/27/06</u> . | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/27/06 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 57, 75, 77 and 80.

After review and reconsideration, claims 63, 66-68 are rejoined with claims 53-55, 64, 70, 72-74, 78-79, 81-82, in view that the nucleic acids of claims 63, 66-68 are a species of the nucleic acid of claims 53-55, 64, 70, 72-74, 78-79, 81-82.

Accordingly, claims 53-55, 63-64, 66-68, 70, 72-74, 78-79, 81-82 are being examined.

NEW REJECTIONS BASED ON NEW CONSIDERATION

Claim Rejections - 35 USC § 101, Utility

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 53-55, 63-64, 66-68, 70, 72-74, 78-79, 81-82 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 53-55, 70 are drawn to an isolated nucleic acid that comprises or consists of the complete complement of SEQ ID NO:1 or 2, wherein said nucleic acid, when introduced into a cell line that expresses a polynucleotide comprising SEQ ID NO:1 or 2, or which encodes a peripheral-type benzodiazepine receptor protein having a mutant threonine at position 147 and a mutant arginine at position 162, and having residues 27-169 of SEQ ID NO:3, inhibits the expression of said polynucleotide.

Claims 63-64 are drawn to the nucleic acid of claim 53, which is comprised in a proteoliposome containing viral envelope receptor proteins (claim 63), or which is present in a vector (claim 64).

Claims 66-68 are drawn to the nucleic acid of claim 53, which is contained in a carrier (claim 66), wherein said carrier is a cytokine or polylysine-glycoprotein carrier (claim 67), or wherein the nucleic acid is comprised in a microbead (claim 68).

Claim 72 is drawn to the nucleic acid of claim 64, which is synthesized in a mammalian cell in vitro, following introduction of said vector into said cell.

Claim 73 is drawn to the nucleic acid of claim 72, which is synthesized in an amount effective to inhibit expression of the polynucleotide comprising SEQ ID NO:1 or 2, or which encodes a peripheral-type benzodiazepine receptor protein having a mutant threonine at position 147 and a mutant arginine at position 162, and having residues 27-169 of SEQ ID NO:3 in the cell line.

Claims 74, 78, 79 are drawn to a composition comprising the nucleic acid of claim 53, 81 or 82 (claim 74), wherein the nucleic acid is present in a vector and is synthesized in a

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mammalian cell in vitro, or in a mammary gland cell in vitro, following introduction of said vector into said cell (claims 78, 79).

Claim 81 is drawn to an isolated nucleic acid consisting of SEQ ID NO:1 or 2, or the complete complement thereof.

Claim 82 is drawn to an isolated nucleic acid encoding a peripheral-type benzodiazepine receptor protein having residues 27-169 of SEQ ID NO:3.

The specification discloses that SEQ ID NO:1 or 2 is a mutated, partial cDNA sequence of 652 nucleotides in length of a peripheral-type benzodiazepine receptor (PBR), found in two breast cancer cell lines, wherein the encoded protein has a mutation to threonine at amino acid position 147, or a mutation to arginine at amino acid position 162, respectively (p.15, 16). It is noted that the corresponding deduced, encoded amino acids 27-169 of SEQ ID NO:3 contains both of the two mutated amino acids in only one amino acid sequence (see Sequence listing).

The specification discloses that the more aggressive cell line expresses a higher concentration of PBR (table 1 on page 36). The specification suggests that the fact that the mutations occur in both a highly aggressive and a non-aggressive breast cancer cell line may represent an early event in the progression of this disease (p.48, last paragraph). The specification discloses that inhibition of PBR expression by homologous recombination in a rat tumor cell line reduces the rate of cell proliferation, as compared to the control (Example 7 on pages 45-46). However, the homologous recombination is only to inhibit the expression of PBR in the cell line; there is no indication that the recombination in Example 7 is correlated in any way with the claimed mutation. The specification discloses that PBR expression is found in aggressive metastatic human breast carcinoma tissue using anti-PBR antiserum (Figure 10 legend on page 13).

However, there is no indication that the detected PBR protein in breast carcinoma tissue has the claimed mutation. The specification contemplates the use of PBR for detection, treatment and prognosis of aggressive tumors, in particular, breast cancer (Summary, p.5-10).

It is noted that SEQ ID NO:1 and 2, both consist of 652 nucleotides in length, as compared to a total of 821 nucleotides of the full length wild type human PBR taught by Riond et al, of record.

One cannot determine whether any of the claimed mutations exists in primary or metastatic breast cancer cells *in vivo*, due to the well known cell culture artifact. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al, 1993 (Leukemia and Lymphoma, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al, 1984 (Immunol Ser, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu, 1973 (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently

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change their chromosomal constitutions (see abstract). Tian, J et al, 2004 (Physiol Genomics, 17: 170-182), teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176).

Similarly, Van Dyke D L et al, 2003 (Cancer Genetics and Cytogenetics 241: 137-141), teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments). Zaslav A L et al, 2002 (Amer J Medical Genetics 107: 174-176), teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p. 175, first column, paragraph under Discussion).). Kunkel, P, et al, 2001 (Neuro-oncology 3(2): 82-88), teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract). The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactual chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays For the reasons set forth above, one cannot determine what use is for the claimed mutated PBR nucleic acid

sequences. Further experimentation is required to determine whether the claimed mutated PBR nucleic acid sequences could be use for diagnosis, or treatment of diseases, such as cancer. Therefore, the specification lacks specific and substantial utility.

Further, although specification discloses that PBR expression is found in aggressive metastatic human breast carcinoma tissue using anti-PBR antiserum, one cannot determine whether the detected PBR is the encoded protein of the mutated or wild type PBR.

Thus, neither the specification nor any art of record teaches a utility for any of the mutated PBR nucleic acids claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

In the absence of any disclosed relationship between the claimed mutated PBR polynucleotides and the encoded polypeptides thereof and any disease or disorder and the lack of any correlation between the claimed mutated PBR polynucleotides and the encoded polypeptides thereof with any known disease or disorder, and further in view that any potential diagnostic or therapeutic utility is not yet known and has not yet been disclosed, the utility is not substantial. Further research is necessary to determine what use is for the claimed mutated PBR polynucleotides or the encoded polypeptides thereof. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

For reasons set forth above the disclosure satisfies none of the three criteria of a specific, substantial, and credible utility. *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the

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Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.’)

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed mutated PBR polynucleotides. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112 First Paragraph, Enablement, New Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-55, 63-64, 66-68, 70, 72-74, 78-79, 81-82 are also rejected under 35 U.S.C.

112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
June 28, 2006


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER